REMARKS/ARGUMENTS

Claims 58-62 are pending in this application. Applicants thank the Examiner for withdrawing the double patenting rejection and the rejection under 35 U.S.C. §112, second paragraph. The remaining rejections under 35 U.S.C. §101, 35 U.S.C. §112, first paragraph, 35 U.S.C. §102, and 35 U.S.C. §103 are addressed below.

I. Priority

Applicants respectfully maintain the position that the specification provides the support required to establish utility for the claimed antibodies, based upon the gene amplification data for the nucleic acid encoding the PRO274 polypeptide, for the reasons previously set forth in Applicants' response filed on September 14, 2004. The gene amplification assay (Example 114) was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in International Application No. PCT/US00/03565, and that the present application is therefore entitled to at least an effective filing date of **February 11, 2000.**

II. Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-62 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility." (Page 2 of the instant Office Action).

Claims 58-62 are further rejected under 35 U.S.C. §112, first paragraph allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 9 of the instant Office Action).

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a

patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

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[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO274 polypeptide and the claimed antibodies that bind it for the reasons previously set forth in the Applicants' response filed on September 14, 2004 and below.

First of all, Applicants respectfully submit that the gene amplification assay is well-described in Example 114 of the present application. As previously discussed in Applicants' Response filed September 14, 2004, the nucleic acids encoding PRO274 had a ΔCt value of > 1.0, which is a **more than 2-fold increase**, for primary lung tumors LT4, LT16, and LT18.. PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold, or 2.0-3.1 fold amplification in three different human primary lung tumors. Therefore, Applicants have clearly shown that the gene encoding the PRO274 polypeptide is amplified in a well-established and quantitative assay.

The Examiner asserts that "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO274." The Examiner further asserts that "it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

skilled artisan to be predictive of increased mRNA and polypeptide levels." (Page 4 of the instant Office Action).

Applicants respectfully submit that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Applicants have shown that the gene encoding PRO274 demonstrated significant amplification, from 2.0-3.1 fold, in three lung tumors. As explained in the Declaration of Dr. Audrey Goddard (submitted with the Response filed September 14, 2004):

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample **is significant** and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. (Emphasis added).

By referring to the 2.0-fold to 3.1-fold amplification of the PRO274 gene in lung tumors as "very small" the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Applicants respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state that:

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Thus, barring evidence to the contrary, Applicants maintain that the 2.2 to 6.5-fold amplification disclosed for the PRO1317 gene is significant and forms the basis for the utility claimed herein.

Applicants further emphasize that they have shown significant DNA amplification in three out of the lung tumor samples in Table 9, Example 114 of the instant specification. The fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. For example, the article by Hanna and Mornin (submitted with the Response filed September 14, 2004), discloses that the known breast cancer marker HER-2/neu is "amplified and/or

overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1). In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO274 gene is amplified in three lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO274 is considered significant is what lends support to its usefulness as a tumor marker.

The Examiner asserts that "it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production." (Page 3 of the instant Office Action). In support of these assertions, the Examiner refers to Pennica *et al.* and contends that " Pennica *et al.* was cited as evidence showing a lack of correlation between gene (DNA) amplification and mRNA levels." The Examiner further refers to Gygi et al., and asserts that "Gygi et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels." (Page 4 of the instant Office Action).

Applicants respectfully submit that, for the reasons previously set forth in Applicants' response filed September 14, 2004, Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Applicants further submit that, as discussed in Applicants' response filed September 14, 2004, Gygi *et al.* never indicate that a correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient for **accurately** predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract). Contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels (Emphasis added). Thus, the Gygi data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Furthermore, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. First, the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Applicants' Response filed September 14, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application (submitted with Applicants' Response filed September 14, 2004), shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Thus, taken together, all of the submitted evidence supports Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

The Examiner contends that "Ornoft *et al.* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Ornoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO274 in the instant specification. That is, it is not clear whether or not PRO274 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Ornoft *et al.* is not clear." (Pages 5-6 of the instant Office Action). The Examiner further alleges, "Hyman *et al.* also used CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* also do not support utility of the polypeptides of the instant invention." (Page 6 of the instant Office Action). The Examiner further alleges that "Pollack *et al*, also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack *et al.* did not investigate polypeptide levels. Therefore, Pollack *et al.* also do not support the asserted utility of the claimed invention." (Page 6 of the instant Office Action).

In Ornoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas.

Orntoft *et al.* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Orntoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Orntoft *et al.* also studied the relationship between altered mRNA and protein levels using 2D-PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO274 is in a gene cluster region of a chromosome. (See page 5 of the instant Office Action). Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Applicants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome."

(See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner further asserts that "none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics" (Page 6 of the instant Office Action). Applicants respectfully point out that Hyman *et al.* conducted additional studies of one of the genes found to be amplified, HOXB7, and found "**a clinical association between HOXB7 amplification and poor patient prognosis**." (Page 6244, col.1 to col.2; emphasis added). Thus the results of Hyman *et al.* confirm that genes which are amplified in tumors have prognostic utility. The Examiner's attention is also respectfully directed to the final paragraph of Pollack *et al.*, wherein the authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor, and for prognostic uses directed to that type of tumor.

With respect to the correlation between mRNA expression and protein levels, the Examiner asserts that the Polakis Declaration is insufficient to overcome the rejection of claims 58-62 since it is limited to a discussion of data regarding the correlation of mRNA levels and

polypeptide levels and not gene amplification levels. The Examiner asserts that the Declaration does not provide data such that the Examiner can independently draw conclusions. (Page 7 of the instant Office Action).

Applicants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles. Applicants emphasize that the opinions expressed in the Polakis Declaration, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[19]

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[18] *In re Rinehart,* 531 F.2d 1084, 189 U.S.P.Q. 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 U.S.P.Q. 881 (Fed. Cir. 1985).

[19] *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)).

Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[20]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[21] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

In response to the evidence provided in the Polakis Declaration, the Examiner cites Hu *et al.* in support of the assertion that "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." (Page 7 of the instant Office Action).

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships."

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[20] *In re Alton, supra.*

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not of gene amplification data. Hence, their findings would not be directly applicable to gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (Emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column).

It often happens in scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusions based on a very unreliable standard and that their research does not provide any meaningful information regarding the correlation between microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown a lack of correlation between microarray data and the biological significance of cancer genes. To the contrary, the evidence of record demonstrates that although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO274 polypeptide and the claimed antibodies that bind it have utility in the diagnosis of cancer.

Further, Applicants have submitted Dr. Ashkenazi's Declaration (with the Response filed September 14, 2004) to show that simultaneous testing of gene amplification and gene product

over-expression enables more accurate tumor classification, even if the gene product (the protein) is not over expressed. Such experiments are carried out with the HER-2/neu protein in order to select patients for treatment with Herceptin monoclonal antibody therapy, as described in the Hanna paper, submitted with the Response filed September 14, 2004. Thus the PRO274 polypeptide has utility in conducting such testing, regardless of whether or not the PRO274 polypeptide is overexpressed.

The Examiner asserts that this is not an acceptable utility because "the gene product o the instant invention has not been demonstrated to be involved in cancer." (Page 9 of the instant Office Action). To the contrary, Applicants have clearly shown that the gene encoding the PRO274 polypeptide is amplified in at least three primary lung tumors. Therefore, the PRO274 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration. The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna paper as experiments involving further characterization of the PRO274 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO274 polypeptide, but the tumors in which the gene encoding PRO274 is amplified. Testing of tumor markers such as PRO274 is useful for tumor categorization even if the tested marker is not itself the intended therapeutic target. The PRO274 polypeptide is therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

In view of the above, Applicants have demonstrated a specific, substantial and credible asserted utility for the PRO274 polypeptide and the claimed antibodies that bind it.

Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed antibodies at the time of filing. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of Claims 58-62 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

III. Claim Rejections Under 35 U.S.C. §102(b)

Claims 58-62 remain rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270 (dated July 14, 2000).

Applicants submit that, as discussed above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement Appellants rely on the gene amplification results (Example 114) to establish a credible, substantial and specific asserted utility for the PRO274 polypeptide and the claimed antibodies that bind it. These results were first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000. As discussed above, the disclosure of the instant application, which is similar to that of the earlier-filed application (PCT/US00/03565), provides the support required under 35 U.S.C. §112 for the subject matter of the instant claims. Accordingly, Applicants submit that the subject matter of the instant claims is disclosed in the manner provided by 35 U.S.C. §112 in PCT/US00/03565. Therefore, the effective filing date of this application is February 11, 2000, the filing date of PCT/US00/03565.

The scientific journal article by Ho *et al.*was published on July 14, 2000, which is over five months after the effective filing date of the instant application; hence Ho *et al.* is not prior art.

Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 58-62 under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*

IV. Claim Rejections Under 35 U.S.C. §103(a)

Claims 59-62 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Immunology, The Immune System in Health and Disease, Third Edition, Janeway, And Travers, Ed., 1997. As discussed above, the article by Ho *et al.* is not prior art to the pending claims of the present application. Accordingly, withdrawal of the rejection of Claims 58-62 under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below. Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C9**).

Respectfully submitted,

Date: August 31, 2005

By: _____
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